

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 29725P WO	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/EP2004/003238	International filing date (day/month/year) 26/03/2004	(Earliest) Priority Date (day/month/year) 28/03/2003
Applicant BIOPHARM GESELLSCHAFT ZUR BIOTECHNOLOGISCHEN...		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.



The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (See Box II).

3. ☐ **Unity of invention is lacking** (see Box III).

4. With regard to the title,

the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

5. With regard to the abstract,

the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regards to the drawings,

- a. the figure of the **drawings** to be published with the abstract is Figure No. 1



as suggested by the applicant.



as selected by this Authority, because the applicant failed to suggest a figure.



as selected by this Authority, because this figure better characterizes the invention.

- b. ☐ none of the figures is to be published with the abstract.

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Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)

The present invention relates to an osteoinductive material comprising a matrix material with morphogenetic protein(s) absorbed on inner or outer surfaces of this matrix material, wherein the osteoinductive material is obtainable by contacting the matrix material and the morphogenic protein(s) under conditions of pH and ionic concentration to keep protein stable and dissolved in a solution until dried and thereby allowing that the matrix material becomes evenly coated with the morphogenic protein(s)

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Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: —
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 26-29 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

 International Application No
 PCT/EP2004/003238

 A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 A61L27/34 A61L27/56 C07K14/475

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

 Minimum documentation searched (classification system followed by classification symbols)
 IPC 7 A61L C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 118 043 A (DINGELDEIN ELVIRA ET AL) 12 September 2000 (2000-09-12) claims 1,7-13,19	1-29
A	WO 94/15653 A (GENENTECH INC) 21 July 1994 (1994-07-21) claims 1-4,9,10,17	1-29

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- * & * document member of the same patent family

Date of the actual completion of the international search

22 September 2004

Date of mailing of the international search report

04/10/2004

Name and mailing address of the ISA

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Heck, G

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP2004/003238

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 6118043	A	12-09-2000	DE 4121043 A1	07-01-1993
			AT 176161 T	15-02-1999
			AU 652839 B2	08-09-1994
			AU 1854692 A	07-01-1993
			CA 2072244 A1	27-12-1992
			CZ 9201946 A3	13-01-1993
			DE 59209624 D1	11-03-1999
			EP 0520237 A2	30-12-1992
			ES 2128330 T3	16-05-1999
			HU 65499 A2	28-06-1994
			IE 922067 A1	30-12-1992
			JP 7171211 A	11-07-1995
			JP 2003093495 A	02-04-2003
			MX 9203253 A1	31-03-1994
			NO 922511 A	28-12-1992
			PL 295001 A2	28-12-1992
			RU 2062622 C1	27-06-1996
			ZA 9204780 A	28-04-1993
WO 9415653	A	21-07-1994	AT 153535 T	15-06-1997
			AU 671721 B2	05-09-1996
			AU 6026294 A	15-08-1994
			CA 2151486 A1	21-07-1994
			DE 69403439 D1	03-07-1997
			DE 69403439 T2	23-10-1997
			DK 679097 T3	22-12-1997
			EP 0679097 A1	02-11-1995
			ES 2105641 T3	16-10-1997
			GR 3024277 T3	31-10-1997
			JP 3347144 B2	20-11-2002
			JP 8505548 T	18-06-1996
			WO 9415653 A1	21-07-1994
			US 5422340 A	06-06-1995

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/EP2004/003238

International filing date (day/month/year)
26.03.2004

Priority date (day/month/year)
28.03.2003

International Patent Classification (IPC) or both national classification and IPC
A61L27/34, A61L27/56, C07K14/475

Applicant
BIOPHARM GESELLSCHAFT ZUR BIOTECHNOLOGISCHEN...

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY****Box No. I Basis of the opinion**

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☒ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☒ in written format
 - ☐ in computer readable form
 - c. time of filing/furnishing:
 - ☒ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

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Box No. II Priority

1. ☒ The following document has not been furnished:

☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 26-29

because:

- ☒ the said international application, or the said claims Nos. 26-29 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the whole application or for said claims Nos.
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
 - the written form ☐ has not been furnished
 - ☐ does not comply with the standard
 - the computer readable form ☐ has not been furnished
 - ☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.
- ☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

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Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-25
	No: Claims	-
Inventive step (IS)	Yes: Claims	-
	No: Claims	1-25
Industrial applicability (IA)	Yes: Claims	1-25
	No: Claims	-

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Since claims 26-29 are directed to a method of treatment of the human or animal body by surgery/therapy, they relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. For the assessment of the subject-matter of present claims 26-29 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States.

Therefore, no opinion will be formulated with respect to the subject-matter of claims 26-29 (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The following document (D1) cited in the International search report is referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1: US 6,118,043 A (Nies B. et al.)

Novelty

Document D1 discloses (cf. claims 1, 7-13, 19) a bone replacement material comprising a porous matrix and fibroblast growth factor (FGF) adsorbed thereon. The material is prepared by impregnating the porous matrix with a solution of FGF followed by drying. The subject-matter of claims 1-25 of the present application differs from the disclosure of D1 by the choice of pH and ionic concentration of the morphogenetic protein solution and is therefore novel according to Article 33(2) PCT.

Inventive Step

Document D1, which is considered to represent the most relevant prior art, discloses (claims 1, 7-13, 19) the impregnation of porous implants with a solution of 50 µg FGF to provide a bone replacement material having a biological activity as close as possible to that of endogenous bone transplantation.

In view of D1, the objective technical problem underlying the present application can be formulated as to provide osteoinductive matrix materials for use in the pharmaceutical field which are homogeneously coated with morphogenetic proteins.

The solution proposed in the present application is a porous osteoinductive material comprising a matrix material having morphogenetic protein(s) adsorbed on inner or outer surfaces thereon, which can be obtained by selecting a pH and an ionic concentration of the solution that avoid precipitation of the morphogenetic proteins.

The expression "contacting the matrix material and the morphogenetic protein(s) under suitable conditions to keep the protein stable and dissolved in a solution until dried" in claim 1 refers to a desirable result without indicating the technical features necessary to obtain it. This leads to a lack of clarity of the claim (Article 6 PCT). The technical contribution of the present invention is not the theoretical finding that a complete dissolution of the morphogenetic protein allows a more homogeneous coating of the matrix material, but the realisation how to enhance both protein stability and solubility during the coating process, which is attainable by selection and control of the pH and low ionic concentrations using suitable buffers/solvents or specific additives (cf. description, p. 7, l. 28-31 and p. 9, l. 4-14). These features should be included in claim 1 to make the claim clear.

Due to the lack of the above-mentioned essential features in claim 1, the subject-matter of claims 1-25 is at present not considered to involve an inventive step according to Article 33(3) PCT. Should the Applicant, however, include those features into claim 1, the following statement would apply:

Since the relation between the pH and low ionic concentration of the morphogenetic protein solution on the one hand and the solubility of the morphogenetic proteins on the other hand is unexpected and allows to obtain a more homogeneous coating of the matrix material, the subject-matter of claims 1-25 is based on an inventive activity according to Article 33(3) PCT.